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Pharmacokinetics and Metabolism of Allopurinol Riboside

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There are no safe and effective oral drugs to treat leishmaniasis and Chagas' disease. The safety, pharmacokinetics, and metabolism of single and multiple oral doses of allopurinol riboside, an investigational antiparasitic agent, were evaluated in a randomized, double-blinded, placebo-controlled study in 32 healthy male volunteers, at levels up to 25 mg/kg q.i.d. for 13 doses. No significant toxicity was detected. Allopurinol riboside peaks in plasma 1.6 hours after administration, has an elimination half-life of 3 hours, and steady-state concentrations in the therapeutic range. However, in contrast to preclinical studies in dogs (plasma levels proportional to oral doses up to 200 mg/kg), we found that plasma levels were unexpectedly low and did not rise with increasing dose. Furthermore, allopurinol and oxypurinol (unanticipated metabolites) were detected at levels proportional to the dose of allopurinol riboside. We present a model that includes incomplete absorption, metabolism of residual drug by enteric flora, and absorption of bacterial metabolites to explain these findings in humans. (CLIN PHARMACOL THER 1991;49:506-14.)

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PHARMACOKINETICS AND  
METABOLISM OF ALLOPURINOL  
RIBOSIDE

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# Pharmacokinetics and metabolism of allopurinol riboside

There are no safe and effective oral drugs to treat leishmaniasis and Chagas' disease. The safety, pharmacokinetics, and metabolism of single and multiple oral doses of allopurinol riboside, an investigational antiparasitic agent, were evaluated in a randomized, double-blinded, placebo-controlled study in 32 healthy male volunteers, at levels up to 25 mg/kg q.i.d. for 13 doses. No significant toxicity was detected. Allopurinol riboside peaks in plasma 1.6 hours after administration, has an elimination half-life of 3 hours, and steady-state concentrations in the therapeutic range. However, in contrast to preclinical studies in dogs (plasma levels proportional to oral doses up to 200 mg/kg), we found that plasma levels were unexpectedly low and did not rise with increasing dose. Furthermore, allopurinol and oxypurinol (unanticipated metabolites) were detected at levels proportional to the dose of allopurinol riboside. We present a model that includes incomplete absorption, metabolism of residual drug by enteric flora, and absorption of bacterial metabolites to explain these findings in humans. (CLIN PHARMACOL THER 1991;49:506-14.)

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Allopurinol riboside, a human metabolite of allopurinol,<sup>1</sup> is an experimental chemotherapeutic agent active in vitro and in animals against the parasitic protozoa that cause leishmaniasis and Chagas' disease.<sup>2,3</sup> These diseases occur in millions of people on a world-

wide basis and may be lethal if not treated. The existing drugs include pentavalent antimonials, pentamidine, amphotericin B, and nifurtimox. These agents typically require multiple parenteral doses, are expensive, and have toxicities that rival those of the diseases themselves. Furthermore, drug-resistant organisms are emerging. For these reasons, a safe and orally effective new drug would have considerable clinical importance.

Both allopurinol and allopurinol riboside enter the purine salvage pathway in *Leishmania* and *Trypanosoma cruzi* (Fig. 1) and ultimately form 4-aminopyrazolopyrimidine ribonucleotide triphosphate, a highly toxic analog of adenosine triphosphate that is incorporated into ribonucleic acid.<sup>4,5</sup> In mammalian tissues, neither allopurinol nor its riboside undergoes this cytotoxic conversion, hence the selective antiparasitic toxicity.<sup>6</sup> However, in mammalian tissues, allopurinol (unlike allopurinol riboside) is rapidly and extensively converted by xanthine oxidase to oxypurinol,<sup>1,6</sup> which has little antiparasitic activity.<sup>7</sup> To avoid this host-mediated inactivation, allopurinol riboside rather than allopurinol is being developed as an antiparasitic drug.

These studies were undertaken to evaluate the safety, pharmacokinetics, and metabolism of orally administered allopurinol riboside in healthy male

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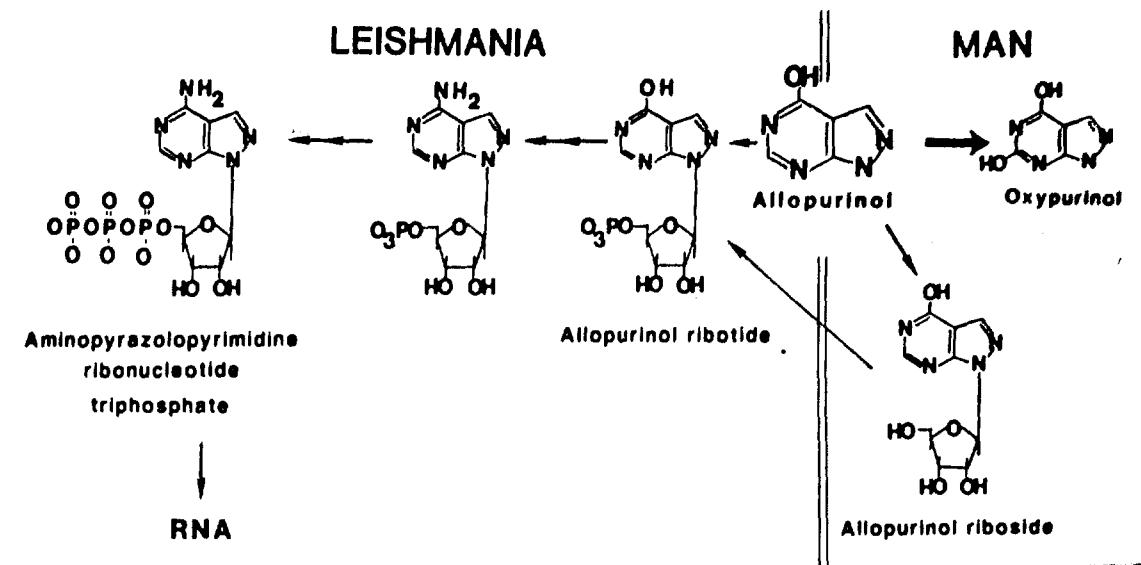
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**Fig. 1.** Allopurinol metabolism in humans and *Leishmania*. Allopurinol is a close structural analog of hypoxanthine. In humans most allopurinol is converted by xanthine oxidase to oxypurinol; about 10% is metabolized to allopurinol riboside. Neither allopurinol nor allopurinol riboside generates ribonucleotides. In *Leishmania*, however, allopurinol and allopurinol riboside enter the purine salvage pathway. Intermediates accumulate in millimolar concentrations and generate aminopyrazolopyrimidine ribonucleotide triphosphate, a toxic analog of adenosine triphosphate that is incorporated into the ribonucleic acid (RNA) of the parasite.<sup>4,5</sup>

volunteers. Preliminary findings were reported previously.<sup>8</sup> In the course of these studies several interesting findings not anticipated from preclinical experiments led us to postulate a model in which the enteric absorption of allopurinol riboside in humans is limited.

## METHODS

**Volunteers.** Healthy men were recruited through newspaper advertisements and accepted into the studies if detailed health history, physical examination, serum chemistry and hematologic results, urinalysis, electrocardiogram, and chest x-ray were normal, if they were within 10% of ideal body weight for height, and if they were not chronic users of any drugs or allergic to allopurinol. Of 253 men who responded, 34 were enrolled. Of these, one failed to return for the follow-up visits and one had abnormal liver function test results immediately before the first dose of drug. Of the 32 who completed the studies, 20 were white, 11 were black, and one was Oriental. The average age was 28 years; the age range was from 18 to 48 years. Written informed consent was obtained from each participant, and the studies were approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

**Drugs.** Allopurinol riboside and matching placebo were provided by the Burroughs Wellcome Company as white powders in colorless gelatin capsules (259 mg/capsule).

**Single-dose study.** All subjects were admitted for 4 days to the Clinical Research Center of the Johns Hopkins Hospital and then followed up for 2 weeks as outpatients. Doses of 0 (placebo), 5, 10, 15, or 20 mg/kg were administered to two individuals at each level, and 25 mg/kg was administered to five volunteers, four of whom completed the protocol. An unblinded investigator was responsible for randomization and drug or placebo administration. Randomization was determined by use of a table of random numbers.

Safety monitoring included nondirected interviews for symptoms and regular periodic measurements of vital signs, hematocrit level, total and differential white blood cell count, platelet count, prothrombin time and serum electrolytes, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, uric acid, and chemical and microscopic urinalyses. Venous blood samples for drug and metabolite determinations were drawn twice before and ½, 1, 2, 4, 6, 8, 10, 12, and 24 hours and 1 and 2 weeks after drug or placebo administration. Voided urine for drug, metabolite, and cre-

atinine determinations was collected before and for 0 to 3, 3 to 6, 6 to 9, 9 to 12, 12 to 24, and 24 to 48 hours after drug or placebo administration. Single untimed urine samples were obtained 1 and 2 weeks after drug administration.

**Multiple-dose study.** Subjects were admitted to the Clinical Research Center for a 5-day period and then followed up for 2 weeks as outpatients. Seven dosage levels were tested: 250, 500, 750, 1000, 1250, 1500, and 1750 mg (4.0 to 25.0 mg/kg). At each level, 13 doses of allopurinol riboside were administered on a q.i.d. schedule (7 AM, noon, 5 PM, and 10 PM) for 4 days. Two volunteers were evaluated at each level, and no volunteer was treated more than once. Four additional volunteers received 1500 mg (18.9 to 23.5 mg/kg) allopurinol riboside q.i.d. for 25 doses during a period of 7 days.

Safety monitoring was comparable to that in the single-dose study. Venous blood for drug and metabolite determinations was drawn twice before, 20, 45, and 75 minutes and 2, 3, and 5 hours after the first dose, and just before doses 4, 5, 6, 8, 9, 10, and 12. Samples were also taken just before, and 20, 45, and 75 minutes and 2, 3, 5, 8, 12, 15, and 24 hours after the final dose of allopurinol riboside. Voided urine was collected before and for 24 hours after the first dose, and from 0 to 2, 2 to 5, 5 to 8, and 8 to 24 hours after the final dose of drug. For the four subjects who received 25 doses of allopurinol riboside, the schedule of venous blood sampling after the first and last doses was unchanged, but additional levels were drawn just before doses 4, 5, 6, 9, 10, 13, 14, 17, 18, 21, 22, 23, and 24, and samples were taken 45 and 75 minutes after dose 23. Urine was collected and pooled for 12 hours before the first dose and for 0 to 24 hours after dose 25.

**Sample collection and assay.** Ten-milliliter venous blood samples were collected in heparinized tubes, immediately chilled on ice, and centrifuged at 1000g for 10 minutes at 4° C. Plasma was withdrawn and frozen at -40° C until analysis. Subjects were asked to void immediately before drug administration, or before the beginning of a sampling interval, and at the end of the sampling interval. Voided urine was refrigerated until the collection interval was complete. Total volume was measured and a 10 ml portion was frozen at -40° C until analysis. Urine samples and perchloric acid extracts of plasma were analyzed for uric acid, hypoxanthine, xanthine, allopurinol, oxypurinol, and allopurinol riboside, by means of automated high performance liquid chromatography (HPLC) according to the method of Kramer and Feldman,<sup>9</sup> with the follow-

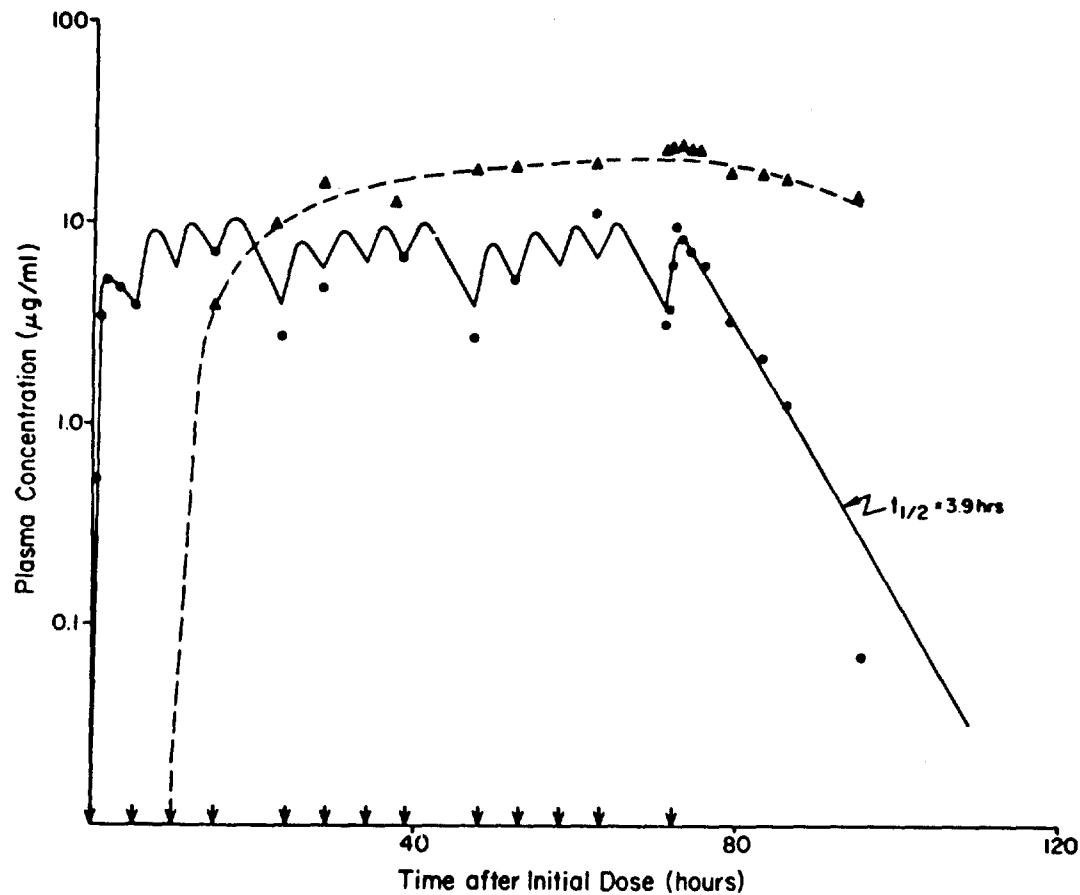
ing modifications. Equipment included a Waters WISP autoinjector (Waters Instruments, Inc., Rochester, Minn.), Whatman Partisil PXS-10/25 ODS-3 C<sub>18</sub> reverse-phase column (Whatman Laboratory Products Inc., Clifton, N.J.), two-channel Command Control Module, Constametric pumps, and Spectromonitor III detectors at 254 and 280 nm (LDC Division, Riviera Beach, Fla.). Samples (50 µl each) were eluted at 1 ml/min in 50 mmol/L ammonium phosphate buffer, pH 5.3, with a 30-minute gradient of 1% to 18% acetonitrile. A solution of mixed standards was prepared from stock solutions that had been calibrated individually by ultraviolet absorbance. A standard curve (from five dilutions containing 0.15 to 25 µg/ml of each compound) was generated at the start and end of the samples from each subject, and one dilution of mixed standards was run after every seven unknown samples. All samples contained *N*-acetyl-*p*-aminophenol as an internal standard. Unknown samples were quantitated by interpolation from standard curves, with the integrated ultraviolet peak areas.

**Pharmacokinetic calculations.** The blood concentration-time data were fitted to a series of exponential models by an iterative nonlinear regression program with a nonweighted least squares criterion of fit, as described in detail previously.<sup>10</sup> This is a noncompartmental analysis, with hybrid parameters in a model-independent series of equations. The program was adapted to and run on a Tektronix 4051 graphics computing system (Tektronix, Inc., Beaverton, Ore.). The observed data showed a reasonable fit to a biexponential function (Fig. 2).

Peak concentration and time to peak for each curve were calculated by differentiation, and the area under the plasma concentration-time curve (AUC) was calculated by integration of the regression equations. Renal clearances were calculated from total urinary excretion and AUC for 48 hours after drug administration in the single-dose study and for 24 hours after the final dose in the multiple-dose study.

## RESULTS

**Assay.** The automated HPLC method proved rapid and reproducible. From a single analysis, uric acid, hypoxanthine, xanthine, oxypurinol, allopurinol, and allopurinol riboside were quantitated (in 85 determinations, the mean retention times relative to *N*-acetyl-*p*-aminophenol [28.5 ± 1.5 minutes] were 0.238, 0.298, 0.332, 0.415, 0.472, and 0.663, respectively). Recoveries were linear between 0.2 and 50 µg/ml. In more than 100 determinations the SD was less than



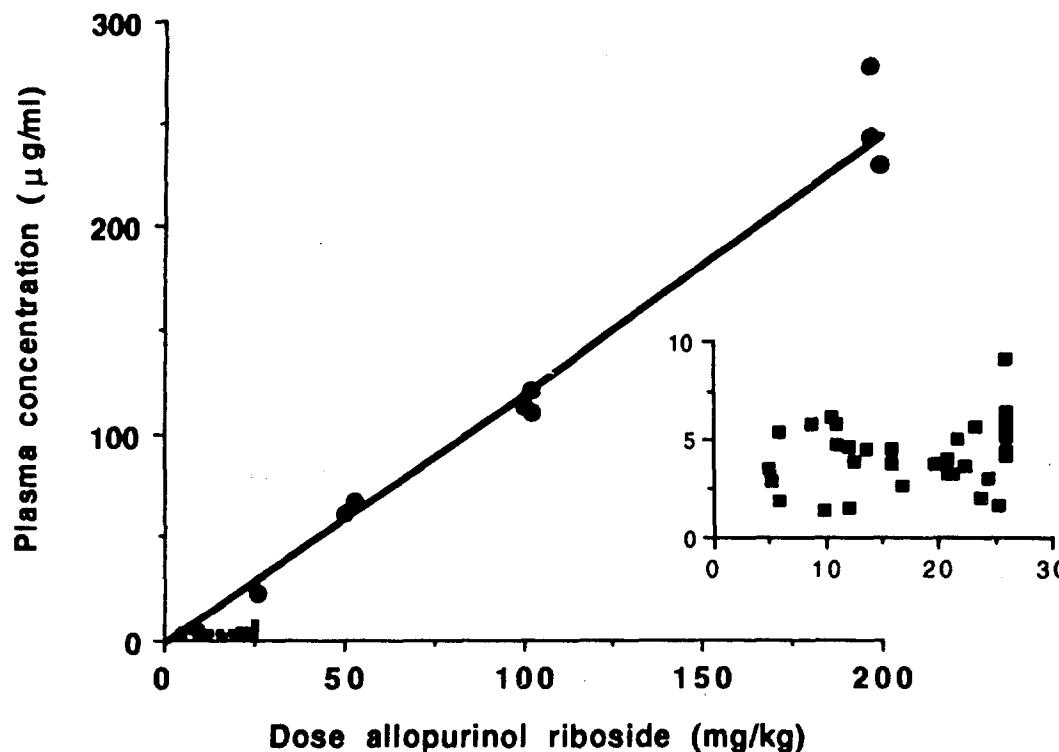
**Fig. 2.** Nonlinear regressions of plasma levels of allopurinol riboside (circles) and oxypurinol (triangles) after 13 doses of 1500 mg (22.5 mg/kg) allopurinol riboside. Allopurinol riboside was given on a q.i.d. schedule, as noted by arrows on the time axis. Points represent the observed data from one volunteer, and the graph was generated by the curve-fitting program. Plasma levels of allopurinol riboside conform to a biexponential model and there is no evidence of drug accumulation. Oxypurinol first appears 10 hours after the initial dose of allopurinol riboside and reaches steady-state levels by the third day.

15% of the mean for allopurinol riboside, 10% for oxypurinol, and 8% for allopurinol.

**Clinical factors.** Minor symptoms, including headache, dizziness, and loose stools, were reported by five volunteers who received allopurinol riboside; although not reported by placebo recipients, these complaints were not dose related and required no intervention. One subject who received 750 mg (11.2 mg/kg) q.i.d. had a clinically significant<sup>11</sup> elevation of alanine aminotransferase levels (79 IU/L; normal level <33 IU/L) 2 weeks after the final dose of allopurinol riboside. His aspartate aminotransferase, bilirubin, and alkaline phosphatase values were not elevated significantly. He had no symptoms or signs of hepatitis, and his alanine aminotransferase levels were normal 6 days later. In most subjects in the multiple-dose study there was a decrease in serum uric acid levels to less than 4.2 mg/dl (normal level 4.2 to 8.8 mg/dl).

**Pharmacokinetics and metabolism.** In the single-dose study, plasma levels of allopurinol riboside peaked between 1 and 2 hours after drug administration, with an elimination half-life ( $t_{1/2}$ ) of about 3 hours (Table I); comparable results were found in the multiple-dose studies (Table I; Fig. 2). Surprisingly, peak plasma levels did not exceed 9 µg/ml, and no correlation between the dose of allopurinol riboside and peak plasma levels could be detected (Fig. 3). There was a similar lack of correlation between dose of allopurinol riboside and either AUC or total urinary excretion of drug (data not shown).

At steady state, in subjects receiving 1500 mg allopurinol riboside q.i.d., up to 41% of the administered dose of allopurinol riboside appeared in the urine as allopurinol riboside (10% to 29%), oxypurinol (5% to 10%), and allopurinol (0% to 2%). Oxypurinol and allopurinol appeared in plasma more than 4 and



**Fig. 3.** Plasma concentrations of allopurinol riboside as a function of dose. Volunteers from both the single- and multiple-dose studies are included (squares, enlarged in *insert*). Peak plasma levels after the first dose of allopurinol riboside are plotted. There is no apparent increase in plasma levels with increasing drug doses ( $R < 0.2$ ). In contrast, in preclinical studies with dogs, plasma levels were proportional to the orally administered dose (circles). In dogs, allopurinol riboside levels at 2 hours are about one half the peak values. Nevertheless, drug concentrations 2 hours after administration in dogs are more than twice the peak values in humans.

**Table I.** Plasma pharmacokinetic parameters of allopurinol riboside

Study	Time to peak (hr)*	Peak concentration (µg/ml)*	$t_{1/2}$ (hr)†
Single dose	$1.58 \pm 0.56$	$4.25 \pm 1.37$	$3.04 \pm 0.79$
Multiple dose	$1.96 \pm 0.88$	$3.22 \pm 1.29‡$	$4.20 \pm 1.66$

Values were obtained by noncompartmental analysis and represent mean values  $\pm$  SD of data from all dosage levels.

\*After first dose in multiple-dose study.

†After final dose in multiple-dose study.

‡Mean ratio of final/initial peak concentrations is 1.8.

usually 10 to 16 hours after the oral administration of allopurinol riboside (Fig. 2). The plasma levels of oxyuric acid and allopurinol were dependent on the dose of allopurinol riboside administered (Fig. 4). At allopurinol riboside doses of 1500 mg q.i.d., oxyuric acid levels did not exceed 28 µg/ml in plasma or 610 µg/ml in urine. The renal clearances of allopurinol riboside, oxyuric acid, and creatinine are compiled in Table II.

Plasma levels of endogenous purines (hypoxanthine, xanthine, and uric acid) were monitored during the multiple-dose study. In most subjects, by 48 hours after the initial dose of allopurinol riboside, hypoxan-

thine and xanthine levels had risen and uric acid levels had fallen. These effects were most marked at higher doses, but paired analyses of pretreatment and post-treatment levels in all subjects who received multiple doses of allopurinol riboside showed statistically significant changes (Fig. 5).

## DISCUSSION

Allopurinol riboside, in doses up to 25 mg/kg q.i.d. for 4 days or 23.5 mg/kg q.i.d. for 7 days, appears to be clinically safe and well tolerated. No consistent subjective side effects were noted, and the one clini-

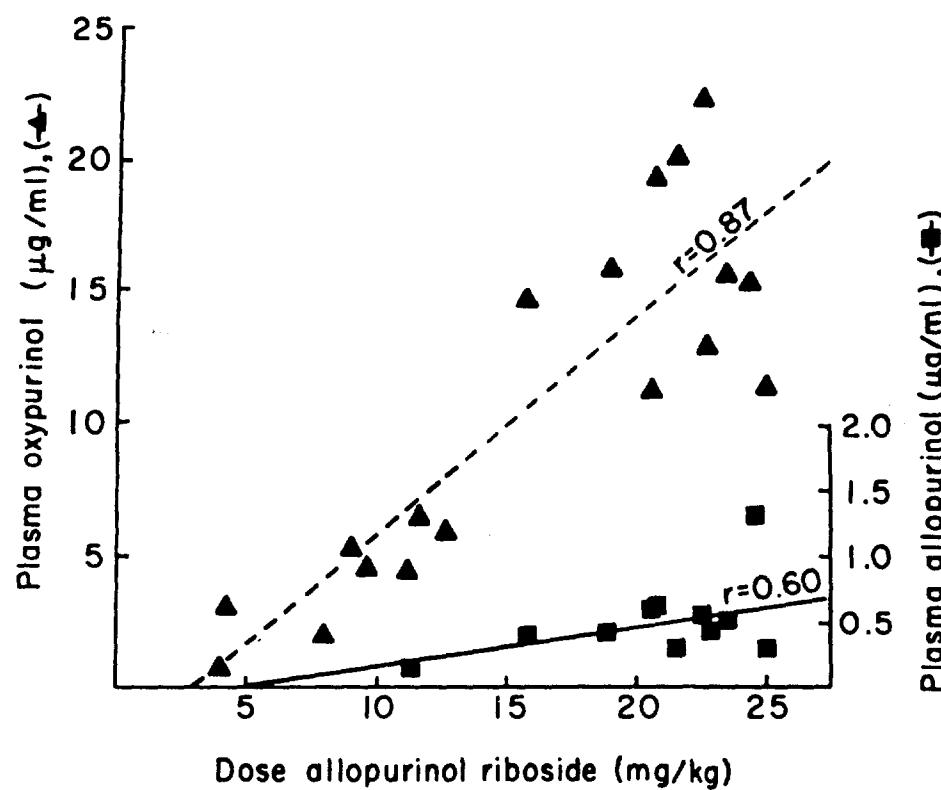


Fig. 4. Plasma levels of oxypurinol (triangles) and allopurinol (squares) as a function of allopurinol riboside dose. Volunteers received the indicated doses of allopurinol riboside on a q.i.d. schedule. Plasma metabolite levels were measured on days 3 and 4, until 3 hours after the final dose of allopurinol riboside, and averaged.

ically significant laboratory change, an isolated elevation in alanine aminotransferase level, occurred 2 weeks after the final dose of allopurinol riboside and may not have been drug related. These studies are shorter than the 6-week regimen that may be required for therapy. However, our findings are corroborated by the known safety of long-term treatment with allopurinol (which generates allopurinol riboside) in humans.

The kinetics of allopurinol riboside after oral administration are relatively simple, with no evidence of accumulation after multiple doses, and a  $t_{1/2}$  that is unaffected by the dosage level or number of doses administered (Table I; Fig. 2). The drug appears promptly in plasma after oral administration and peaks within 2 hours. When given on a q.i.d. schedule, the plasma levels in the six volunteers who received 13 or 25 doses of 1500 mg allopurinol riboside fluctuated between a mean peak level of  $6.2 \pm 2.9 \mu\text{g}/\text{ml}$  and a mean trough level of  $2.4 \pm 0.9 \mu\text{g}/\text{ml}$ . These values are within the ranges reported to be effective in vitro against the amastigotes of *Leishmania* ( $\text{ID}_{90}$ , 0.6 to 20  $\mu\text{g}/\text{ml}$ ) and *T. cruzi* ( $\text{IC}_{50}$ , about 5  $\mu\text{g}/\text{ml}$ ).<sup>2,3</sup>

There were two unexpected findings in these studies

Table II. Renal clearances

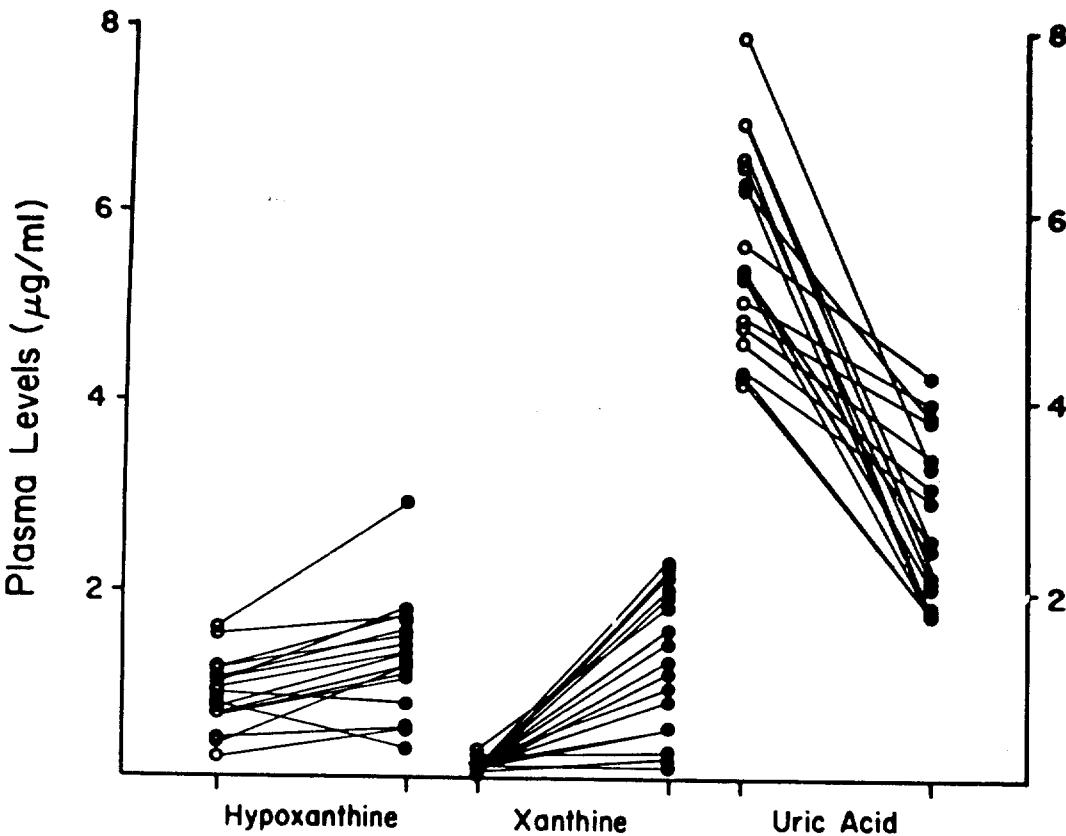
Compound	Renal clearance (ml/min)	
	This study*	Reported previously
Allopurinol riboside	$263 \pm 95$	—
Oxypurinol	$13.1 \pm 9.4$	13-15 <sup>†</sup>
Creatinine	$108 \pm 23$	108 <sup>‡</sup>

\*Values represent mean values  $\pm$  SD from all subjects in both studies. Drug and metabolite clearances were calculated from total urinary excretion and area under the plasma concentration-time curve for 48 hours after a single dose or 24 hours after the final dose in the multiple-dose study. Creatinine clearances were derived from the weight, age, and serum creatinine levels for each subject, according to the equation of Cockcroft and Gault.<sup>18</sup>

<sup>†</sup>References 12 and 19.

<sup>‡</sup>Obtained by linear regression of age versus creatinine clearance from data.<sup>18</sup>

that are likely to be related. The first was the relatively low peak plasma levels (most did not exceed 6  $\mu\text{g}/\text{ml}$ ), which did not rise appreciably with increasing doses of allopurinol riboside (Fig. 3). In contrast, in preclinical studies with dogs, plasma levels were dose related at oral doses up to 200 mg/kg (Fig. 3). Furthermore, at 25 mg/kg, plasma levels in the dog 2 hours after drug administration were more than twice



**Fig. 5.** Changes in endogenous purine levels with allopurinol riboside administration. Eighteen volunteers received 13 or 25 doses of allopurinol riboside on a q.i.d. schedule. Subjects from all dosage levels (4 to 25 mg/kg) are included. For each volunteer, five pretreatment values were averaged (open circles) and about nine posttreatment values were averaged (closed circles) from day 3 until 3 hours after the final dose. Increases in hypoxanthine and xanthine and decreases in uric acid levels were statistically significant at the  $p < 0.001$  level in paired *t* test analyses.

the highest peak plasma levels achieved in humans (Fig. 3). Because plasma levels in the dog peak before 2 hours, this discrepancy is even greater than depicted. (At 50 mg/kg in dogs, peak levels are twice those measured at 2 hours.) The second unexpected finding was the conversion of allopurinol riboside to allopurinol and, to a much greater extent, to oxypurinol. Cleavage of allopurinol riboside by human purine nucleoside phosphorylase is very slow.<sup>6</sup> In animals, particularly rodents, allopurinol riboside is converted to oxypurinol riboside and oxypurinol by aldehyde oxidase. However, tissue levels of aldehyde oxidase in humans and dogs are negligible.<sup>12</sup> For these reasons, production of oxypurinol in humans was not anticipated. Indeed, this was the rationale for developing allopurinol riboside rather than allopurinol as an antiparasitic agent.

A model to explain both unexpected results can be proposed. In humans, allopurinol riboside may be absorbed from the gut by a saturable transport mecha-

nism, the capacity of which is exceeded by the administered doses. Oxypurinol may then originate from free allopurinol, which is cleaved from unabsorbed allopurinol riboside by enteric bacteria, absorbed, and oxidized in the tissues by xanthine oxidase. There are several lines of evidence to support this model. First, plasma levels of allopurinol riboside are not increased by a sixfold increase in dose (Fig. 3). Second, in human tissues, mechanisms for achieving the conversion of allopurinol riboside to oxypurinol are unfavorable. Third, free allopurinol is detected in plasma and urine. Fourth, both peak plasma levels (Fig. 4) and total urinary excretion of allopurinol and oxypurinol increase with dose. This is expected if a fixed amount of drug is absorbed from the increasing doses, leaving increasing amounts of unabsorbed allopurinol riboside in the gut. Fifth, there is a delay of at least 5, and usually 10 to 16, hours after the administration of allopurinol riboside before oxypurinol appears in plasma (Fig. 2). After oral administration of allopurinol to humans, oxy-

purinol appears almost at once.<sup>13</sup> Finally, human colonic flora, particularly anaerobic group D streptococci (but not *Escherichia coli*), readily convert allopurinol riboside to allopurinol in vitro (Nelson DJ, Desjardins RE, Bushby SRM. Unpublished data, November 1983). Interestingly, plasma levels of allopurinol and oxypurinol extrapolate to zero at a dose of 3 to 5 mg/kg (Fig. 4), which may represent the upper limit of enteric drug transport.

The appearance of oxypurinol raises some practical issues. In these studies the highest plasma and urine levels of oxypurinol were 28 and 510  $\mu\text{g}/\text{ml}$ , respectively. Oxypurinol blood concentrations as high as 20 to 30  $\mu\text{g}/\text{ml}$  are observed in patients taking 900 to 1500 mg allopurinol/day and are not associated with any particular risk.<sup>14</sup> Excretion of oxypurinol in the urine at levels in excess of 300 to 400  $\mu\text{g}/\text{ml}$  may constitute some risk because of the poor solubility of this compound<sup>15</sup>; however, none of the volunteers had crystalluria or evidence of renal damage. Although allopurinol riboside does not inhibit xanthine oxidase, both allopurinol and oxypurinol do. As a result, hypoxanthine and xanthine (the natural substrates of xanthine oxidase) accumulate, and uric acid (its product) is depleted. These changes in endogenous purines were seen in the multiple-dose study (Fig. 5) and were most marked at the upper dosage levels in subjects with high oxypurinol concentrations. Inasmuch as hypoxanthine and, to a lesser extent, xanthine in vitro can partially reverse the antiparasitic activity of allopurinol,<sup>4,7</sup> inhibition of xanthine oxidase in patients receiving allopurinol riboside may adversely affect drug efficacy.

The calculated renal clearance of oxypurinol (13  $\text{ml}/\text{min}$ ) compares well with values reported previously<sup>1,13</sup> and suggests tubular reabsorption. On the other hand, the mean clearance of allopurinol riboside was 263  $\text{ml}/\text{min}$ , which is more than twice the mean creatinine clearance of 108  $\text{ml}/\text{min}$  and suggests active renal tubular excretion (Table II).

These studies pose several challenges to the use of allopurinol riboside in humans. Nevertheless the drug continues to have promise: it appears to be safe, particularly in comparison with the drugs currently available, and it has recently proved efficacious in patients with *L. braziliensis panamensis* infections.<sup>16</sup> (Five of nine patients showed clinical improvement and three were cured.) Unlike the situation with allopurinol, the undesirable conversion to oxypurinol can largely be prevented (without sacrificing allopurinol riboside plasma levels) simply by reducing the dose of drug administered (Fig. 4). Furthermore, if the proposed

model is correct, parenteral administration of allopurinol riboside would preclude oxypurinol formation entirely. The relatively low plasma levels achievable in humans are attributable to both limited absorption and brisk clearance. Coadministration with probenecid blocks the renal clearance of allopurinol riboside in humans and more than doubles plasma allopurinol riboside levels (Shapiro TA. Unpublished data, November 1984). Further increases in plasma levels could be achieved by parenteral administration of allopurinol riboside or, preferably, by use of an oral pro-drug. There is growing precedent for the successful use of oral pro-drugs such as 6-deoxyacyclovir (a metabolic precursor of acyclovir<sup>17</sup>) to facilitate the absorption of purine nucleosides in humans. In view of the pressing need for new agents to treat leishmaniasis and Chagas' disease, and the promising preliminary results with allopurinol riboside, efforts should be made to circumvent the difficulties this drug presents and to continue its development.

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